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<b>(21) International Application Number:</b> PCT/US97/15044 <b>(22) International Filing Date:</b> 26 August 1997 (26.08.97)  <b>(30) Priority Data:</b> 60/024,980 30 August 1996 (30.08.96) US 08/915,918 21 August 1997 (21.08.97) US  <b>(71) Applicant:</b> ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).  <b>(72) Inventor:</b> EFENDIC, Suad; Stjamvagen 16B, S-181 34 Lidingo (SE).  <b>(74) Agent:</b> STEVENSON, Robert, W.; Brinks Hofer Gilson & Lione, NBC Tower, Suite 3600, 455 North Cityfront Plaza Drive, Chicago, IL 60611-5599 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> USE OF GLP-1 OR ANALOGS IN TREATMENT OF MYOCARDIAL INFARCTION  <b>(57) Abstract</b>  This invention provides a method of reducing mortality and morbidity after myocardial infarction. GLP-1, a GLP-1 analog, or a GLP-1 derivative, is administered at a dose effective to normalize blood glucose.		

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USE OF GLP-1 OR ANALOGS IN TREATMENT  
OF MYOCARDIAL INFARCTION

Background Of The Invention

1. Field of the Invention. This invention relates  
5 to a method of reducing mortality and morbidity after  
myocardial infarction in diabetic patients.

2. Background Information. Morbidity and mortality  
from cardiovascular disease is higher in patients with  
manifest diabetes or impaired glucose tolerance compared to  
10 patients without those disorders. Diabetics account for up to  
24% of the total number of patients admitted to coronary care  
units for suspect infarction, whereas they constitute only  
about 5% of the general population [Malmberg and Rydén;  
Fuller J.H., *Diabet. Metab.* 19:96-99 (1993)]. In-hospital  
15 mortality of diabetic patients with myocardial infarction is  
twice that of non-diabetics [Hamsten A., et al., *J. Int. Med.*  
736:1-3 (1994) 236 Suppl.; Malmberg K. and Rydén L., *Eur.*  
*Heart J.* 9:256-264 (1988)]. Diabetics experience more  
morbidity and die more often in the post-acute recovery phase,  
20 mostly due to fatal re-infarction and congestive heart failure  
[Malmberg and Rydén; Stone P., et al., *J. Am. Coll. Cardiol.*  
14:49-57 (1989); Karlson B.W., et al., *Diabet. Med.* 10(5):449-  
54 (1993); Barbash G.I., et al., *J. Am. Coll. Cardiol.* 22:707-  
713 (1993)]. The difference in mortality and morbidity  
25 between diabetics and non-diabetics following myocardial  
infarction persists, despite reduction in the incidence of  
morbidity and mortality following acute myocardial infarction  
[Granger C.B., et al., *J. Am. Coll. Cardiol.*, 21(4):920-5  
(1993); Grines C., et al., *N. Engl. J. Med.* 328:673-679  
30 (1993)].

Factors responsible for the poor prognosis among  
diabetic patients with acute myocardial infarction may act  
before, during, or after the acute event. They include  
diffuse coronary atheromatosis, with more advanced and  
35 widespread coronary artery disease, which, together with a  
possible diabetic cardiomyopathy, may contribute to a high  
prevalence of congestive heart failure. Autonomic neuropathy  
with impaired pain perception and increased resting heart rate  
variability may also be of importance. A coronary thrombus is

an essential part of an evolving infarction, and notably, platelet activity, coagulation, and fibrinolytic functions have been found to be disturbed in diabetic patients [Davi G., et al., *New England. J. Med.*, 322:1769-1774 (1990)].

5 Exaggerated metabolic disturbances in diabetics may play an important role. Myocardial infarction causes a reduction in circulating insulin, a dramatic increase in adrenergic tone, and the release of stress hormones, such as, cortisone, catecholamines, and glucagon, that together enhance  
10 hyperglycemia and stimulate lipolysis. The released free fatty acids further injure the myocardium via several mechanisms, and excessive oxidation of free fatty acids may possibly damage nonischemic parts of the myocardium [Rodrigues B., et al., *Cardiovascular Research*, 26(10):913-922 (1992)].

15 Palliative measures to normalize blood glucose and to control the metabolic cascade that exacerbates infarct damage in diabetics are needed. In a recent trial, improved metabolic care of diabetic patients during acute myocardial infarction, including carefully-monitored infusion of insulin  
20 and glucose, and post-acute tight regulation of blood glucose by subcutaneous multidose insulin treatment lowered mortality during the year following myocardial infarction by 30% compared with a control group of diabetics who did not receive insulin treatment unless deemed clinically necessary  
25 [Malmberg, K, et al., *J. Am. College Cardiology*, 26:57-65 (1995)].

Insulin infusion, however, creates the potential for hypoglycemia, which is defined as blood glucose below 0.3 mM. Hypoglycemia increases the risk of ventricular arrhythmia and  
30 is a dangerous consequence of insulin infusion. An algorithm for insulin infusion for diabetics with myocardial infarction was developed to prevent hypoglycemia [Hendra, T.J., et al., *Diabetes Res. Clin. Pract.*, 16:213-220 (1992)]. However, 21% of the patients developed hypoglycemia under this algorithm.  
35 In another study of glucose control following myocardial infarction, 18% of the patients developed hypoglycemia when infused with insulin and glucose [Malmberg, K.A., et al., *Diabetes Care*, 17:1007-1014 (1994)].

Insulin infusion also requires frequent monitoring of blood glucose levels so that the onset of hypoglycemia can be detected and remedied as soon as possible. In patients receiving insulin infusion in the cited study [Malmberg, 1994], blood glucose was measured at least every second hour, and the rate of infusion adjusted accordingly. Thus, the safety and efficacy of insulin-glucose infusion therapy for myocardial infarct patients depends on easy and rapid access to blood glucose data. Such an intense need for monitoring blood glucose places a heavy burden on health care professionals, and increases the inconvenience and cost of treatment. As a result, cardiac intensive care units often do not allot resources for optimizing blood glucose levels in diabetics with acute myocardial infarction, as might be obtained by intravenous administration of insulin. Considering the risks and burdens inherent in insulin infusion, an alternate approach to management of blood glucose during acute myocardial infarction in diabetics is needed.

The incretin hormone, glucagon-like peptide 1, abbreviated as GLP-1, is processed from proglucagon in the gut and enhances nutrient-induced insulin release [Krcymann B., et al., *Lancet* 2:1300-1303 (1987)]. Various truncated forms of GLP-1, are known to stimulate insulin secretion (insulinotropic action) and cAMP formation [see, e.g., Mojsov, S., *Int. J. Peptide Protein Research*, 40:333-343 (1992)]. A relationship between various in vitro laboratory experiments and mammalian, especially human, insulinotropic responses to exogenous administration of GLP-1, GLP-1(7-36) amide, and GLP-1(7-37) acid has been established [see, e.g., Nauck, M.A., et al., *Diabetologia*, 36:741-744 (1993); Gutniak, M., et al., *New England J. of Medicine*, 326(20):1316-1322 (1992); Nauck, M.A., et al., *J. Clin. Invest.*, 91:301-307 (1993); and Thorens, B., et al., *Diabetes*, 42:1219-1225 (1993)]. GLP-1(7-36) amide exerts a pronounced antidiabetogenic effect in insulin-dependent diabetics by stimulating insulin sensitivity and by enhancing glucose-induced insulin release at physiological concentrations [Gutniak M., et al., *New England J. Med.* 326:1316-1322 (1992)]. When administered to non-insulin dependent diabetics, GLP-1(7-36) amide stimulates insulin

release, lowers glucagon secretion, inhibits gastric emptying and enhances glucose utilization [Nauck, 1993; Gutniak, 1992; Nauck, 1993].

5 The use of GLP-1 type molecules for prolonged therapy of diabetes has been obstructed because the serum half-life of such peptides is quite short. For example, GLP-1(7-37) has a serum half-life of only 3 to 5 minutes. GLP-1(7-36) amide has a half-life of about 50 minutes when administered subcutaneously. Thus, these GLP molecules must  
10 be administered as a continuous infusion to achieve a prolonged effect [Gutniak M., et al., *Diabetes Care* 17:1039-1044 (1994)]. In the present invention, GLP-1's short half-life and the consequent need for continuous administration are not disadvantages because the patient is typically bed-ridden,  
15 in a cardiac intensive care unit, where fluids are continuously administered parenterally.

#### Summary Of The Invention

20 The present invention provides a method of reducing mortality and morbidity after myocardial infarction, comprising administering a compound from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives, and pharmaceutically-acceptable salts thereof, at a dose effective to normalize blood glucose, to a patient in need thereof.

25 The present invention provides the benefits of reduction in mortality and morbidity after myocardial infarction observed in combined treatment with glucose and insulin in diabetics during acute myocardial infarction, but without the inconvenient and expensive requirement of frequent  
30 monitoring of blood glucose, interpretation of blood glucose results, and adjustment of insulin dose rate, and without the ever-present risk of hypoglycemia that accompanies insulin infusion.

#### 35 Brief Description of the Drawings

Figure 1 is a graph showing the effect of continuous infusion GLP-1 (7-36) amide on average blood glucose concentration (mM) (—■—) in five NIDDM patients during the night. The graph also depicts the effect of continuous

insulin infusion on average blood glucose concentration (---O---) in the same five NIDDM patients, but on a different night.

Figure 2 is a graph showing the effect of GLP-1 (7-36) amide infusion on average blood glucose concentration (---■---) in five NIDDM patients when infused during the day, for three hours starting at the beginning of each of three meals. The graph also depicts the effect of subcutaneous injection of insulin on average blood glucose concentration (---O---) in the same five NIDDM patients, but on a different day, and with injection shortly before each meal.

#### Detailed Description Of The Invention

"GLP-1" means GLP-1(7-37). By custom in the art, the amino-terminus of GLP-1(7-37) has been assigned number 7 and the carboxy-terminus, number 37. The amino acid sequence of GLP-1(7-37) is well-known in the art, but is presented below for the reader's convenience:

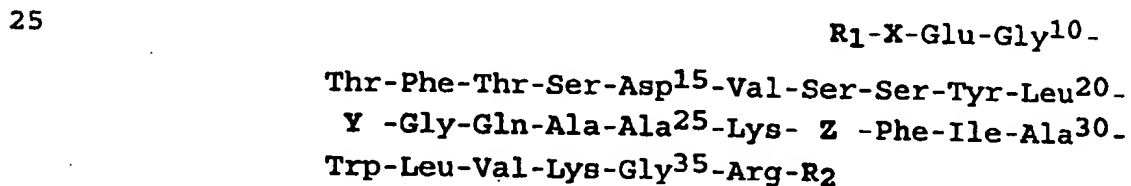
NH<sub>2</sub>-His<sup>7</sup>-Ala-Glu-Gly<sup>10</sup>-  
Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-  
Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Glu-Phe-Ile-Ala<sup>30</sup>-  
Trp-Leu-Val-Lys-Gly<sup>35</sup>-Arg-Gly<sup>37</sup>-COOH

(SEQ ID NO:1)

A "GLP-1 analog" is defined as a molecule having one or more amino acid substitutions, deletions, inversions, or additions compared with GLP-1. GLP-1 analogs known in the art include, for example, GLP-1(7-34) and GLP-1(7-35), GLP-1(7-36), Gln<sup>9</sup>-GLP-1(7-37), D-Gln<sup>9</sup>-GLP-1(7-37), Thr<sup>16</sup>-Lys<sup>18</sup>-GLP-1(7-37), and Lys<sup>18</sup>-GLP-1(7-37). Preferred GLP-1 analogs are GLP-1(7-34) and GLP-1(7-35), which are disclosed in U.S. Patent No. 5,118,666, herein incorporated by reference, and also GLP-1(7-36), which are the biologically processed forms of GLP-1 having insulintropic properties. Other GLP-1 analogs are disclosed in U.S. Patent No. 5,545,618 which is incorporated herein by reference.

A "GLP-1 derivative" is defined as a molecule having the amino acid sequence of GLP-1 or of a GLP-1 analog, but additionally having chemical modification of one or more of its amino acid side groups,  $\alpha$ -carbon atoms, terminal amino group, or terminal carboxylic acid group. A chemical modification includes, but is not limited to, adding chemical moieties, creating new bonds, and removing chemical moieties. Modifications at amino acid side groups include, without limitation, acylation of lysine  $\epsilon$ -amino groups, N-alkylation of arginine, histidine, or lysine, alkylation of glutamic or aspartic carboxylic acid groups, and deamidation of glutamine or asparagine. Modifications of the terminal amino include, without limitation, the des-amino, N-lower alkyl, N-di-lower alkyl, and N-acyl modifications. Modifications of the terminal carboxy group include, without limitation, the amide, lower alkyl amide, dialkyl amide, and lower alkyl ester modifications. Lower alkyl is C<sub>1</sub>-C<sub>4</sub> alkyl. Furthermore, one or more side groups, or terminal groups, may be protected by protective groups known to the ordinarily-skilled protein chemist. The  $\alpha$ -carbon of an amino acid may be mono- or dimethylated.

A preferred group of GLP-1 analogs and derivatives for use in the present invention is composed of molecules of the formula:



(SEQ ID NO:2)

and pharmaceutically-acceptable salts thereof, wherein: R<sub>1</sub> is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,  $\beta$ -hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine; X is selected from the group consisting of Ala, Gly, Val, Thr, Ile, and alpha-methyl-Ala; Y is selected from the group consisting of Glu, Gln,

Ala, Thr, Ser, and Gly; Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly; and R<sub>2</sub> is selected from the group consisting of NH<sub>2</sub>, and Gly-OH; provided that the compound has an isoelectric point in the  
5 range from about 6.0 to about 9.0 and further providing that when R<sub>1</sub> is His, X is Ala, Y is Glu, and Z is Glu, R<sub>2</sub> must be NH<sub>2</sub>.

Numerous GLP-1 analogs and derivatives having an isoelectric point in this range have been disclosed and  
10 include, for example:

GLP-1 (7-36)NH<sub>2</sub>  
Gly<sup>8</sup>-GLP-1 (7-36)NH<sub>2</sub>  
Gln<sup>9</sup>-GLP-1 (7-37)  
D-Gln<sup>9</sup>-GLP-1 (7-37)  
15 acetyl-Lys<sup>9</sup>-GLP-1 (7-37)  
Thr<sup>9</sup>-GLP-1 (7-37)  
D-Thr<sup>9</sup>-GLP-1 (7-37)  
Asn<sup>9</sup>-GLP-1 (7-37)  
D-Asn<sup>9</sup>-GLP-1 (7-37)  
20 Ser<sup>22</sup>-Arg<sup>23</sup>-Arg<sup>24</sup>-Gln<sup>26</sup>-GLP-1 (7-37)  
Thr<sup>16</sup>-Lys<sup>18</sup>-GLP-1 (7-37)  
Lys<sup>18</sup>-GLP-1 (7-37)  
Arg<sup>23</sup>-GLP-1 (7-37)  
Arg<sup>24</sup>-GLP-1 (7-37), and the like [see, e.g., WO  
25 91/11457].

Another preferred group of active compounds for use in the present invention is disclosed in WO 91/11457, and consists essentially of GLP-1(7-34), GLP-1(7-35), GLP-1(7-36), or GLP-1(7-37), or the amide form thereof, and  
30 pharmaceutically-acceptable salts thereof, having at least one modification selected from the group consisting of:

(a) substitution of glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, phenylalanine, arginine, or  
35 D-lysine for lysine at position 26 and/or position 34; or substitution of glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, phenylalanine, lysine, or a D-arginine for arginine at position 36;

(b) substitution of an oxidation-resistant amino acid for tryptophan at position 31;

(c) substitution of at least one of: tyrosine for valine at position 16; lysine for serine at position 18;  
5 aspartic acid for glutamic acid at position 21; serine for glycine at position 22; arginine for glutamine at position 23; arginine for alanine at position 24; and glutamine for lysine at position 26; and

(d) substitution of at least one of: glycine,  
10 serine, or cysteine for alanine at position 8; aspartic acid, glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine for glutamic acid at position 9; serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine,  
15 valine, isoleucine, leucine, methionine, or phenylalanine for glycine at position 10; and glutamic acid for aspartic acid at position 15; and

(e) substitution of glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine,  
20 isoleucine, leucine, methionine, or phenylalanine, or the D- or N-acylated or alkylated form of histidine for histidine at position 7; wherein, in the substitutions is (a), (b), (d), and (e), the substituted amino acids can optionally be in the D-form and the amino acids substituted at position 7 can  
25 optionally be in the N-acylated or N-alkylated form.

Because the enzyme, dipeptidyl-peptidase IV (DPP IV), may be responsible for the observed rapid *in vivo* inactivation of administered GLP-1, [see, e.g., Mentlein, R., et al., *Eur. J. Biochem.*, 214:829-835 (1993)], administration  
30 of GLP-1 analogs and derivatives that are protected from the activity of DPP IV is preferred, and the administration of Gly<sup>8</sup>-GLP-1(7-36)NH<sub>2</sub>, Val<sup>8</sup>-GLP-1(7-37)OH, a-methyl-Ala<sup>8</sup>-GLP-1(7-36)NH<sub>2</sub>, and Gly<sup>8</sup>-Gln<sup>21</sup>-GLP-1(7-37)OH, or pharmaceutically-acceptable salts thereof, is more preferred.

35 The use in the present invention of a molecule claimed in U.S. Patent No. 5,188,666, which is expressly incorporated by reference, is preferred. Such molecule is selected from the group consisting of a peptide having the amino acid sequence:

NH<sub>2</sub>-His<sup>7</sup>-Ala-Glu-Gly<sup>10</sup>-  
 Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-  
 Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Glu-Phe-Ile-Ala<sup>30</sup>-  
 Trp-Leu-Val-X

5

(SEQ ID NO:3)

wherein X is selected from the group consisting of Lys and Lys-Gly; and a derivative of said peptide, wherein said peptide is selected from the group consisting of: a  
 10 pharmaceutically-acceptable acid addition salt of said peptide; a pharmaceutically-acceptable carboxylate salt of said peptide; a pharmaceutically-acceptable lower alkylester of said peptide; and a pharmaceutically-acceptable amide of said peptide selected from the group consisting of amide,  
 15 lower alkyl amide, and lower dialkyl amide.

Another preferred group of molecules for use in the present invention consists of compounds, claimed in U.S. Patent No. 5,512,549, which is expressly incorporated herein by reference, of the general formula:

20

R<sup>1</sup>-Ala-Glu-Gly<sup>10</sup>-  
 Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-  
 Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Xaa-Glu-Phe-Ile-Ala<sup>30</sup>-  
 Trp-Leu-Val-Lys-Gly<sup>35</sup>-Arg-R<sup>3</sup>

25

|  
 R<sup>2</sup>

(SEQ ID NO:4)

and pharmaceutically-acceptable salts thereof, wherein R<sup>1</sup> is  
 30 selected from the group consisting of 4-imidazopropionyl, 4-imidazoacetyl, or 4-imidazo- $\alpha,\alpha$ dimethyl-acetyl; R<sup>2</sup> is selected from the group consisting of C<sub>6</sub>-C<sub>10</sub> unbranched acyl, or is absent; R<sup>3</sup> is selected from the group consisting of Gly-OH or NH<sub>2</sub>; and, Xaa is Lys or Arg, may be used in present invention.

35

More preferred compounds of SEQ ID NO:4 for use in the present invention are those in which Xaa is Arg and R<sup>2</sup> is C<sub>6</sub>-C<sub>10</sub> unbranched acyl.

Highly preferred compounds of SEQ ID NO:4 for use in the present invention are those in which Xaa is Arg, R<sup>2</sup> is C<sub>6</sub>-C<sub>10</sub> unbranched acyl, and R<sup>3</sup> is Gly-OH.

5 More highly preferred compounds of SEQ ID NO:4 for use in the present invention are those in which Xaa is Arg, R<sup>2</sup> is C<sub>6</sub>-C<sub>10</sub> unbranched acyl, R<sup>3</sup> is Gly-OH, and R<sup>1</sup> is 4-imidazopropionyl.

The most preferred compound of SEQ ID NO:4 for use in the present invention is that in which Xaa is Arg, R<sup>2</sup> is C<sub>8</sub> unbranched acyl, R<sup>3</sup> is Gly-OH, and R<sup>1</sup> is 4-imidazopropionyl.

The use in the present invention of a molecule claimed in U.S. Patent No. 5,120,712, which is expressly incorporated by reference, is highly preferred. Such molecule is selected from the group consisting of a peptide having the amino acid sequence:

NH<sub>2</sub>-His<sup>7</sup>-Ala-Glu-Gly<sup>10</sup>-  
Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-  
Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Glu-Phe-Ile-Ala<sup>30</sup>-  
Trp-Leu-Val-Lys-Gly<sup>35</sup>-Arg-Gly<sup>37</sup>-COOH

20

(SEQ ID NO:1)

and a derivative of said peptide, wherein said peptide is selected from the group consisting of: a pharmaceutically-acceptable acid addition salt of said peptide; a  
25 pharmaceutically-acceptable carboxylate salt of said peptide; a pharmaceutically-acceptable lower alkylester of said peptide; and a pharmaceutically-acceptable amide of said peptide selected from the group consisting of amide, lower alkyl amide, and lower dialkyl amide.

30 The use of GLP-1(7-36) amide, or a pharmaceutically-acceptable salt thereof, in the present invention is most highly preferred. The amino acid sequence of GLP-1(7-36) amide is:

NH<sub>2</sub>-His<sup>7</sup>-Ala-Glu-Gly<sup>10</sup>-  
35 Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-  
Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Glu-Phe-Ile-Ala<sup>30</sup>-  
Trp-Leu-Val-Lys-Gly<sup>35</sup>-Arg-NH<sub>2</sub>

(SEQ ID NO:5)

Methods for preparing the active compound used in the present invention, namely, GLP-1, an GLP-1 analog, or a GLP-1 derivative used in the present invention are well-known, and are described in U.S. Patent Nos. 5,118,666, 5,120,712, and 5,523,549, which are incorporated by reference.

The amino acid portion of the active compound used in the present invention, or a precursor thereto, is made either by 1) solid-phase synthetic chemistry; 2) purification of GLP molecules from natural sources; or 3) recombinant DNA technology.

Solid phase chemical synthesis of polypeptides is well known in the art and may be found in general texts in the area such as Dugas, H. and Penney, C., *Bioorganic Chemistry*, Springer-Verlag, New York (1981), pp. 54-92, Merrifield, J.M., *Chem. Soc.*, 85:2149 (1962), and Stewart and Young, *Solid Phase Peptide Synthesis*, Freeman, San Francisco (1969) pp. 24-66.

For example, the amino acid portion may be synthesized by solid-phase methodology utilizing a 430A peptide synthesizer (PE-Applied Biosystems, Inc., 850 Lincoln Center Drive, Foster City, CA 94404) and synthesis cycles supplied by PE-Applied Biosystems. BOC-amino acids and other reagents are commercially available from PE-Applied Biosystems and other chemical supply houses. Sequential Boc chemistry using double couple protocols are applied to the starting p-methyl benzhydryl amine resins for the production of C-terminal carboxamides. For the production of C-terminal acids, the corresponding PAM resin is used. Asn, Gln, and Arg are coupled using preformed hydroxy benzotriazole esters. The following side chain protecting groups may be used:

Arg, Tosyl  
Asp, cyclohexyl  
Glu, cyclohexyl  
Ser, Benzyl  
Thr, Benzyl  
Tyr, 4-bromo carbobenzoxy

Boc deprotection may be accomplished with trifluoroacetic acid in methylene chloride. Following

completion of the synthesis the peptides may be deprotected and cleaved from the resin with anhydrous hydrogen fluoride (HF) containing 10% meta-cresol. Cleavage of the side chain protecting group(s) and of the peptide from the resin is  
5 carried out at -5°C to 5°C, preferably on ice for 60 minutes. After removal of the HF, the peptide/resin is washed with ether, and the peptide extracted with glacial acetic acid and lyophilized.

Techniques well-known to the ordinarily-skilled  
10 artisan in recombinant DNA technology may be used to prepare the active compound used in present invention. In fact, recombinant DNA methods may be preferable because of higher yield. The basic steps in recombinant production are:

- 15 a) isolating a natural DNA sequence encoding a GLP-1 molecule or constructing a synthetic or semi-synthetic DNA coding sequence for a GLP-1 molecule,
- 20 b) placing the coding sequence into an expression vector in a manner suitable for expressing proteins either alone or as a fusion proteins,
- 25 c) transforming an appropriate eukaryotic or prokaryotic host cell with the expression vector,
- 30 d) culturing the transformed host cell under conditions that will permit expression of a GLP-1 molecule, and
- e) recovering and purifying the recombinantly produced GLP-1 molecule.

As previously stated, the coding sequences may be  
35 wholly synthetic or the result of modifications to the larger, native glucagon-encoding DNA. A DNA sequence that encodes preproglucagon is presented in Lund, et al., *Proc. Natl. Acad. Sci. U.S.A.* 79:345-349 (1982) and may be used as starting material in the semisynthetic production of the compounds of  
40 the present invention by altering the native sequence to achieve the desired results.

Synthetic genes, the *in vitro* or *in vivo* transcription and translation of which results in the production of a GLP-1 molecule, may be constructed by  
45 techniques well known in the art. Owing to the natural

degeneracy of the genetic code, the skilled artisan will recognize that a sizable yet definite number of DNA sequences may be constructed, all of which encode GLP-1 molecules.

5 The methodology of synthetic gene construction is well-known in the art. See Brown, et al. (1979) *Methods in Enzymology*, Academic Press, N.Y., Vol. 68, pgs. 109-151. The DNA sequence is designed from the desired amino acid sequence using the genetic code, which is easily ascertained by the ordinarily-skilled biologist. Once designed, the sequence  
10 itself may be generated using conventional DNA synthesizing apparatus such as the Model 380A or 380B DNA synthesizers (PE-Applied Biosystems, Inc., 850 Lincoln Center Drive, Foster City, CA 94404).

To express the amino acid portion of a compound used  
15 in the present invention, one inserts the engineered synthetic DNA sequence in any one of many appropriate recombinant DNA expression vectors through the use of appropriate restriction endonucleases. See generally Maniatis et al. (1989) *Molecular Cloning; A Laboratory Manual*, Cold Springs Harbor Laboratory  
20 Press, N.Y., Vol. 1-3. Restriction endonuclease cleavage sites are engineered into either end of the GLP-1 molecule-encoding DNA to facilitate isolation from, and integration into, amplification and expression vectors well-known in the art. The particular endonucleases employed will be dictated  
25 by the restriction endonuclease cleavage pattern of the parent expression vector employed. Restriction sites are chosen to properly orient the coding sequence with control sequences, thereby achieving proper in-frame reading and expression of the protein of interest. The coding sequence must be  
30 positioned to be in proper reading frame with the promoter and ribosome binding site of the expression vector, both of which are functional in the host cell in which the protein is to be expressed.

To achieve efficient transcription of the synthetic  
35 gene, it must be operably associated with a promoter-operator region. Therefore, the promoter-operator region of the synthetic gene is placed in the same sequential orientation with respect to the ATG start codon of the synthetic gene.

A variety of expression vectors useful for transforming prokaryotic and eukaryotic cells are well known in the art. See *The Promega Biological Research Products Catalogue* (1992) (Promega Corp., 2800 Woods Hollow Road, Madison, WI, 53711-5399); and *The Stratagene Cloning Systems Catalogue* (1992) (Stratagene Corp., 11011 North Torrey Pines Road, La Jolla, CA, 92037). Also, U.S. Patent No. 4,710,473 describes circular DNA plasmid transformation vectors useful for expression of exogenous genes in *E. coli* at high levels. These plasmids are useful as transformation vectors in recombinant DNA procedures and

- (a) confer on the plasmid the capacity for autonomous replication in a host cell;
- (b) control autonomous plasmid replication in relation to the temperature at which host cell cultures are maintained;
- (c) stabilize maintenance of the plasmid in host cell populations;
- (d) direct synthesis of a protein product indicative of plasmid maintenance in a host cell population;
- (e) provide in-series restriction endonuclease recognition sites unique to the plasmid; and
- (f) terminate mRNA transcription.

These circular DNA plasmids are useful as vectors in recombinant DNA procedures for securing high levels of expression of exogenous genes.

Having constructed an expression vector for the amino acid portion of a compound used in the present invention, the next step is to place the vector into a suitable cell and thereby construct a recombinant host cell useful for expressing the polypeptide. Techniques for transforming cells with recombinant DNA vectors are well known in the art and may be found in such general references as Maniatis, et al. *supra*. Host cells may be constructed from either eukaryotic or prokaryotic cells.

Prokaryotic host cells generally produce the protein at higher rates and are easier to culture. Proteins expressed in high-level bacterial expression systems characteristically

aggregate in granules or inclusion bodies, which contain high levels of the overexpressed protein. Such protein aggregates typically must be recovered, solubilized, denatured and refolded using techniques well known in the art. See Kreuger, 5 et al. (1990) in *Protein Folding*, Gierasch and King, eds., pgs 136-142, American Association for the Advancement of Science Publication No. 89-18S, Washington, D.C.; and U.S. Patent No. 4,923,967.

Alterations to a precursor GLP-1 or GLP-1 analog amino acid sequence, to produce a desired GLP-1 analog or GLP-1 derivative, are made by well-known methods: chemical modification, enzymatic modification, or a combination of chemical and enzymatic modification of GLP-1 precursors. The techniques of classical solution phase methods and semi- 15 synthetic methods may also be useful for preparing the GLP-1 molecules used in the present invention. Methods for preparing the GLP-1 molecules of the present invention are well known to an ordinarily skilled peptide chemist.

Addition of an acyl group to the epsilon amino group of Lys<sup>34</sup> may be accomplished using any one of a variety of 20 methods known in the art. See *Bioconjugate Chem.* "Chemical Modifications of Proteins: History and Applications" pages 1, 2-12 (1990) and Hashimoto et al., *Pharmaceutical Res.* 6(2):171-176 (1989).

For example, an N-hydroxy-succinimide ester of octanoic acid can be added to the lysyl-epsilon amine using 50% acetonitrile in borate buffer. The peptide can be acylated either before or after the imidazolic group is added. Moreover, if the peptide is prepared recombinantly, acylation 30 prior to enzymatic cleavage is possible. Also, the lysine in the GLP-1 derivative can be acylated as taught in WO96-29342, which is incorporated herein by reference.

The existence and preparation of a multitude of protected, unprotected, and partially-protected, natural and 35 unnatural, functional analogs and derivatives of GLP-1 (7-36)amide and GLP-1 (7-37) molecules have been described in the art [see, e.g., U.S. Pat. No. 5,120,712 and 5,118,666, which are herein incorporated by reference, and Orskov, C., et al.,

*J. Biol. Chem.*, 264(22):12826-12829 (1989) and WO 91/11457 (Buckley, D.I., et al., published August 8, 1991)].

Optionally, the amino and carboxy terminal amino acid residues of GLP-1 derivatives may be protected, or, optionally, only one of the termini is protected. Reactions for the formation and removal of such protecting groups are described in standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York (1973); Green, T.H., "Protective Groups in Organic Synthesis", Wiley, New York (1981); and "The Peptides", Vol. I, Schröder and Lübke, Academic Press London and New York (1965). Representative amino-protecting groups include, for example, formyl, acetyl, isopropyl, butoxycarbonyl, fluorenylmethoxycarbonyl, carbobenzyloxy, and the like. Representative carboxy-protecting groups include, for example, benzyl ester, methyl ester, ethyl ester, t-butyl ester, p-nitro phenyl ester, and the like.

Carboxy-terminal, lower-alkyl-ester, GLP-1 derivatives used in the present invention are prepared by reacting the desired (C<sub>1</sub>-C<sub>4</sub>) alkanol with the desired polypeptide in the presence of a catalytic acid such as hydrochloric acid. Appropriate conditions for such alkyl ester formation include a reaction temperature of about 50°C and reaction time of about 1 hour to about 3 hours. Similarly, alkyl ester derivatives of the Asp and/or Glu residues can be formed.

Preparation of a carboxamide derivative of a compound used in the present invention is formed, for example, as described in Stewart, J. M., et al., *Solid Phase Peptide Synthesis*, Pierce Chemical Company Press, 1984.

A pharmaceutically-acceptable salt form of GLP-1, of a GLP-1 analog, or of a GLP-1 derivative may be used in the present invention. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid,

citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and, especially, hydrochloric acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like. The salt forms are particularly preferred.

A GLP-1, GLP-1 analog, or GLP-1 derivative used in the present invention may be formulated with one or more excipients before use in the present invention. For example, the active compound used in the present invention may be complexed with a divalent metal cation by well-known methods. Such metal cations include, for example,  $Zn^{++}$ ,  $Mn^{++}$ ,  $Fe^{++}$ ,  $Co^{++}$ ,  $Cd^{++}$ ,  $Ni^{++}$ , and the like.

Optionally, the active compound used in the present invention may be combined with a pharmaceutically-acceptable buffer, and the pH adjusted to provide acceptable stability, and a pH acceptable for parenteral administration.

Optionally, one or more pharmaceutically-acceptable anti-microbial agents may be added. Meta-cresol and phenol are preferred pharmaceutically-acceptable anti-microbial

agents. One or more pharmaceutically-acceptable salts may be added to adjust the ionic strength or tonicity. One or more excipients may be added to further adjust the isotonicity of the formulation. Glycerin is an example of an isotonicity-  
5 adjusting excipient.

Administration may be via any route known to be effective by the physician of ordinary skill. Parenteral administration is preferred. Parenteral administration is commonly understood in the medical literature as the injection  
10 of a dosage form into the body by a sterile syringe or some other mechanical device such as an infusion pump. Parenteral routes include intravenous, intramuscular, subcutaneous, intraperitoneal, intraspinal, intrathecal, intracerebroventricular, intraarterial, subarachnoid, and  
15 epidural. Intravenous, intramuscular, and subcutaneous routes of administration of the compounds used in the present invention are more preferred. Intravenous and subcutaneous routes of administration of the compounds used in the present invention are yet more highly preferred. For parenteral  
20 administration, an active compound used in the present invention preferably is combined with distilled water at an appropriate pH.

Additional pharmaceutical methods may be employed to control the duration of action. Controlled release  
25 preparations may be achieved by the use of polymers to complex or absorb the active compound used in the present invention. Extended duration may be obtained by selecting appropriate macromolecules, for example, polyesters, polyamino acids, polyvinylpyrrolidone, ethylenevinyl acetate, methylcellulose, carboxymethylcellulose, or protamine sulfate, and by selecting  
30 the concentration of macromolecules, as well as the methods of incorporation, in order to prolong release. Another possible method to extend the duration of action by controlled release preparations is to incorporate an active compound used in the  
35 present invention into particles of a polymeric material such as polyesters, polyamino acids, hydrogels, poly (lactic acid) or ethylene vinylacetate copolymers. Alternatively, instead of incorporating a compound into these polymeric particles, it is possible to entrap a compound used in the present invention

in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules, respectively, or in colloidal drug delivery systems, for example, liposomes, 5 albumin microspheres, microemulsions, nanoparticles, and nanocapsules, or in macroemulsions. Such teachings are disclosed in *Remington's Pharmaceutical Sciences* (1980).

A diagnosis of "myocardial infarction" is one involving medical judgment, and typically relies on a finding 10 of at least two of the following symptoms and indications:

- 1) chest pain of at least 15 minute duration;
- 2) at least two values of serum creatine kinase and serum creatine kinase B at least two standard deviations above the normal range 10-16 h after 15 onset of symptoms;
- 3) two or more serum lactate dehydrogenase levels that are at least two standard deviations above the normal range within 48-72 hours after onset of symptoms, including an isoenzyme pattern typical of 20 myocardial infarction; and
- 4) development of new Q waves and/or initial ST elevation followed by T-wave inversion in at least two of the 12 standard ECG leads.

The acute phase of myocardial infarction occurs 25 during the first 72 hours after the onset of the symptoms or indications described above. The treatment which is the subject of this invention is given during the acute phase of myocardial infarction, that is, in acute myocardial infarction.

30 A patient in need of the compounds used in the present invention is one who is in the acute phase of myocardial infarction, and who also is incapable of auto-regulation of blood glucose. A patient is incapable of auto-regulation if that patient: 1) was previously diagnosed with 35 insulin-dependent diabetes (IDDM) or non-insulin dependent diabetes (NIDDM), according to the definitions of the National Diabetes Data Group [*Diabetes*, 28:1039-1057 (1979)]; 2) has a blood glucose level greater than 11 mmol/liter, even without a

previous diagnosis of diabetes; or 3) has an abnormal glucose tolerance.

The dose of GLP-1, GLP-1 analog, or GLP-1 derivative effective to normalize a patient's blood glucose level will depend on a number of factors, among which are included, without limitation, the patient's sex, weight and age, the severity of inability to regulate blood glucose, the underlying causes of inability to regulate blood glucose, whether glucose, or another carbohydrate source, is simultaneously administered, the route of administration and bioavailability, the persistence in the body, the formulation, and the potency. Where administration is continuous, a suitable dosage rate is between 0.25 and 6 pmol/kg body weight/min, preferably from about 0.5 to about 1.2 pmol/kg/min. Where administration is intermittent, the dose per administration should take into account the interval between doses, the bioavailability of GLP-1, GLP-1 analog, or GLP-1 derivative, and the level needed to effect normal blood glucose. It is within the skill of the ordinary physician to titrate the dose and rate of administration of GLP-1, GLP-1 analog, or GLP-1 derivative to achieve the desired clinical result.

The present invention will be more readily understood by reference to specific examples, which are provided to illustrate, not to limit, the present invention.

#### Example 1

GLP-1 (7-36) amide was administered by a subcutaneous infusion at a dose rate of 1.2 pmol/kg/hr, for ten hours during the night, to five patients having non-insulin dependent diabetes (NIDDM). As a control, insulin was continuously infused in the same five patients, but on a different day than the GLP-1 (7-36) amide infusion. The rate of insulin infusion was adjusted every two hours to achieve optimum control, and to avoid hypoglycemia. As demonstrated by the data in Table 1, and in Fig. 1, subcutaneous infusion of GLP-1 (7-36) amide nearly normalized blood glucose without inducing hypoglycemia in any of the patients. The metabolic control with GLP-1 (7-36) amide was better than that achieved

by insulin, and the average blood glucose level was lower for GLP-1 (7-36) amide treatment than for the control by a statistically significant amount at 23:00, 0:00, and at 1:00.

- 5 Table 1. Average blood glucose levels for five NIDDM patients continuously infused for ten hours during the night with GLP-1 (7-36) amide. In a control study with the same patients on a different day, insulin was administered by continuous infusion.

10

Hour	GLP-1 Infusion		Insulin Infusion (Control)	
	Average Blood Glucose (mM)	Std. Error (mM)	Average Blood Glucose (mM)	Std. Error (mM)
21:00	7.5	0.45	6.9	0.68
22:00	5.4	0.76	6.6	0.55
23:00	4.1	0.16	5.9	0.98
0:00	4.4	0.23	5.6	0.90
1:00	4.4	0.29	5.1	0.58
2:00	4.8	0.34	5.2	0.58
3:00	5.2	0.41	5.4	0.30
4:00	5.4	0.41	5.7	0.25
5:00	5.8	0.41	6.0	0.30
6:00	6.0	0.45	6.1	0.38
7:00	6.2	0.45	6.1	0.33

### Example 2

During the day, GLP-1 (7-36) amide was infused into five NIDDM patients for three hours during breakfast, lunch, and dinner. The infusion times were 7:30-10:30 (breakfast), 10:30-1:30 (lunch), and 4:30-7:30 (dinner), as indicated in Figure 2. In a control experiment in the same five NIDDM patients conducted on a different day, insulin was injected subcutaneously just before the start of the meals, as indicated in Figure 2. While GLP-1 was infused, the post-prandial glucose excursions observed with insulin injection were eliminated, and normal blood glucose levels were maintained. Immediately after terminating each GLP-1 (7-36) amide infusion, the blood glucose level increased significantly. No untoward side effects of GLP-1 (7-36) amide

were observed. These data indicate that GLP-1 (7-36) amide infusion more effectively controls post-prandial glucose levels than insulin injection, and that the control is effective as long as GLP-1 (7-36) amide infusion is continued.

5  
10 Table 2. Average blood glucose levels for five NIDDM patients infused with GLP-1 (7-36) amide for three hours, beginning at the start of each meal. In a control study with the same patients on a different day, insulin was administered by subcutaneous injection just before each meal. Meals began at 7:30, 10:30, and at 4:30.

Hour	GLP-1 Infusion		Insulin Subcutaneous Injection	
	Average Blood Glucose (mM)	Std. Error (mM)	Average Blood Glucose (mM)	Std. Error (mM)
7:00	5.4	0.35	6.1	0.41
8:00	4.9	0.38	7.0	0.51
9:00	5.7	0.59	9.1	0.74
10:00	5.8	1.06	9.9	0.78
11:00	8.1	0.94	8.2	0.76
12:00	9.4	0.59	6.5	0.74
13:00	7.2	1.18	9.1	0.90
14:00	5.3	1.21	8.1	0.91
15:00	7.2	0.71	7.0	0.87
16:00	10.4	0.26	7.2	0.57
17:00	9.2	1.06	6.5	0.59
18:00	5.7	1.59	7.3	0.65
19:00	6.6	0.94	6.1	0.59
20:00	8.3	0.71	6.0	0.41
21:00	9.3	0.71	6.4	0.44

I claim:

1. A method of reducing mortality and morbidity after myocardial infarction, comprising administering to a patient in need thereof, a compound selected from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives, and  
5 pharmaceutically-acceptable salts thereof, at a dose effective to normalize blood glucose.
2. The method of Claim 1, wherein the compound is administered intravenously.
3. The method of Claim 1, wherein the compound is administered subcutaneously.
4. The method of Claims 2 or 3, wherein the administration is continuous.
5. The method of Claim 4 wherein the rate of  
5 administration of the compound is between 0.25 and 6 pmol/kg/min.
6. The method of Claim 5 wherein the rate of administration of the compound is between 0.5 and 2.4  
10 pmol/kg/min.
7. The method of Claim 5 wherein said rate is between about 0.5 and about 1.2 pmol/kg/min.
8. The method of Claim 2 wherein the intravenous administration is intermittent.
9. The method of Claim 2 wherein the compound is  
15 administered intravenously and also administered by another parenteral route.
10. The method of Claim 9 wherein the other parenteral route is the subcutaneous route.
11. The method of Claim 1 wherein the compound  
20 administered is GLP(7-36) amide, or a pharmaceutically-acceptable salt thereof.
12. A method of reducing morbidity and mortality after myocardial infarction, comprising, administering a  
25 compound that exerts insulintropic activity by interacting with the same receptor, or receptors, with which GLP-1, GLP-1 analogs, and GLP-1 derivatives interact in exerting their insulintropic activity.
13. A method of reducing morbidity and mortality  
30 after myocardial infarction, comprising, administering a

compound that enhances insulin sensitivity by interacting with the same receptor, or receptors, with which GLP-1, GLP-1 analogs, and GLP-1 derivatives interact to enhance insulin sensitivity.

FIG. 1

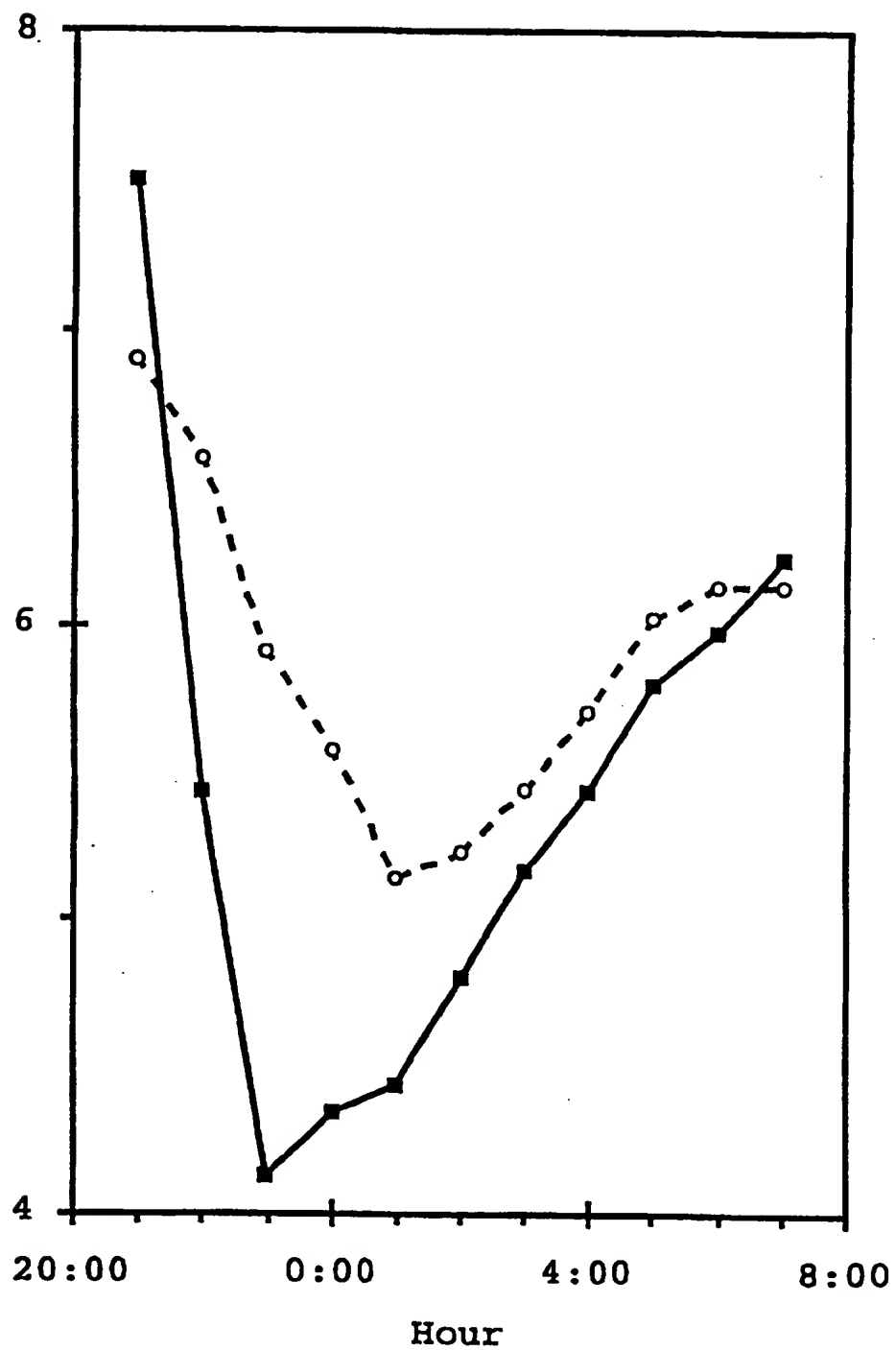
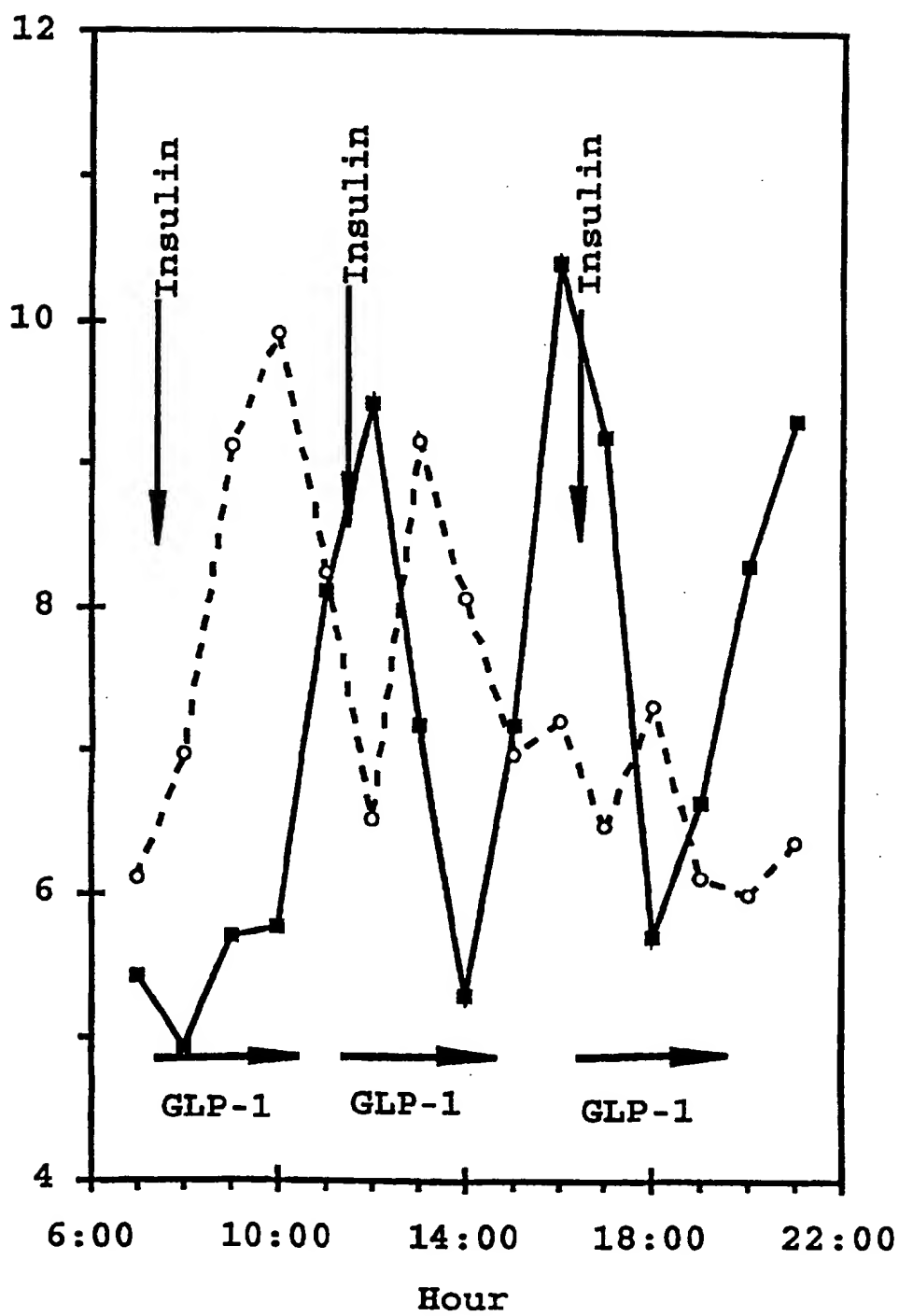


FIG. 2



<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : A61K 38/00 US CL : 514/2 According to International Patent Classification (IPC) r to both national classification and IPC																				
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/2 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched NONE Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS AND CAS ONLINE: gip-1 and myocardial infarction and heart attack																				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>																				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
A,P	US 5,614,492 A (HABENER) 25 March 1997.	1-13																		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"> <tr> <td>* Special categories of cited documents:</td> <td>*T</td> <td>later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>*A* document defining the general state of the art which is not considered to be of particular relevance</td> <td>*X*</td> <td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>*E* earlier document published on or after the international filing date</td> <td>*Y*</td> <td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>*A*</td> <td>document member of the same patent family</td> </tr> <tr> <td>*O* document referring to an oral disclosure, use, exhibition or other means</td> <td></td> <td></td> </tr> <tr> <td>*F* document published prior to the international filing date but later than the priority date claimed</td> <td></td> <td></td> </tr> </table>			* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family	*O* document referring to an oral disclosure, use, exhibition or other means			*F* document published prior to the international filing date but later than the priority date claimed		
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*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																		
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																		
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family																		
*O* document referring to an oral disclosure, use, exhibition or other means																				
*F* document published prior to the international filing date but later than the priority date claimed																				
Date of the actual completion of the international search 10 OCTOBER 1997		Date of mailing of the international search report 31 OCT 1997																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile N. (703) 305-3230		Authorized officer KIMBERLY JORDAN Telephone No. (703) 308-1235																		